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EXAMINER
HUYNH, PHUONG N

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17

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/684,794	YANG ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28-38* is/are pending in the application.

4a) Of the above claim(s) *34-38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 28-38 are pending.

2. In view of the amendment filed 5/22/03, the following rejection remains.

3. Claims 34-38 stand withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected invention.

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 28-33 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Chang *et al* (J Agric Food Chem 47: 61-66, Jan 1999; PTO 892) in view of US Pat No. 4,4324,782 (April 1982, PTO 892), US Pat No. 5,367,054 (of record, Nov 1994; PTO 892) and Akita *et al* (of record, J. of Food Science: 57(3): 629-634; PTO 892).

Chang *et al* teach a preparation method of immunoglobulin Y (IgY) against dental caries bacteria including the steps of: preparing streptococcus mutants antigen as antigen bacteria by separately culturing streptococcus mutans type c and type d in a culture medium such as brain heart infusion broth for the desired concentration of the bacteria such as culturing for 18 hours

and collecting the bacteria by centrifugation and washing the bacteria with sterile saline which is a phosphate buffered saline, pH 7 (See Materials and Methods, in particular). The recitation of culturing 2-3 days is within the purview of one skill in the art at the time the invention was made to varying the duration of culture to obtain sufficient number of bacteria. Chang *et al* teach the immunodominant sugars in the cell walls of S mutans serotype a, c, e, and f are glucose-glucose while those in the cell walls of S mutans serotype b, d and g are glalactose (See page 63, column 1, fourth paragraph, in particular). Chang *et al* teach human dental caries is mainly (over 70%) caused by S. mutans c followed by S. mutans d and that the antibody against c and d must be applied simultaneously to effectively prevent the human dental caries (See page 63, column 1, second to the last paragraph, in particular). Chang *et al* teach adding adjuvant such as Freund's incomplete adjuvant to equal volume of S mutans and mixed homogenously prior to immunizing hens by hypodermic needle injection of S mutans 1 x 10^9 at CFU/ml each time at once a week for 4 weeks intervals to obtain eggs with active antibody (See page 61 Immunization of Hens, in particular). The reference active antibody against S mutans begins to climb in the third week and last about 13 weeks and then decreased gradually to the 23rd week (See Fig 1, page 63, Effect of Immunization Route on Antibody Activity, in particular). Chang *et al* teach the reference IgY are purified by high methoxy pectin method follows by gel filtration using column such as Sephacryl S-300 and eluting the protein peak with phosphate buffer (PBS) containing 0.85% NaCl in 0.01M phosphate. Fractions of each peak are pooled and the antibody activity of the eluates of the reference protein peaks is estimated with ELISA (See page 62, column 2, Gel filtration, Enzyme-linked Immunosorbent Assay (ELISA), Fig 3, in particular). Chang *et al* teach IgY can be lyophilized and store until ready to be use (See column 62, column 1, first full paragraph, in particular). The recitation of collecting and sterilizing said eggs from 20th day after said first hypodermic injection in claim 29(b2) and claim 32(g) are included in this rejection because Chang *et al* teach active antibody against S mutans begins to climb in the third week which is 20 days after immunization and last about 13 weeks and then decreased gradually to the 23rd week (See Fig 1, page 63, Effect of Immunization Route on Antibody Activity, in particular).

The claimed invention in claims 28(a1) and 32(a) differs from the reference only culturing S mutans type c and type d in a culture medium for 2 to 3 days.

The claimed invention in claim 28(a2) and 32(b) differs from the reference only collecting bacteria by centrifugation.

The claimed invention in claim 28(a3) and 32(c) differs from the reference only washing said bacteria 4 to 6 times with 0.05-0.2M of phosphate buffer saline, pH 6-7 and heating at 50-60°C for 25 to 35 minutes.

The claimed invention in claims 28(a4) and 32(d) differs from the reference only that preparation of IgY against dental carries bacteria wherein the dental carries bacteria streptococcus mutans type c and type d is mixed in a ratio of 2:1.

The claimed invention in claims 28(c), differs from the reference only that the preparation of IgY against dental carries bacteria wherein the crude IgY from eggs is extracted by water dilution method instead of high methoxy pectin method.

The claimed invention in claims 28(d) and 32(n) differs from the reference only that the preparation of IgY against dental carries bacteria by applying the crude IgY on "DEAE-Sephadex A50" column and eluting with phosphate buffer containing 0.07 M of NaCl to obtain eluates of the protein peak instead of Sephacryl S-300 column.

The claimed invention in claims 28(e), and 32(o) differs from the reference only that the preparation of IgY against dental carries bacteria by applying said eluates of protein peak on Sephadex G200 column and eluting with phosphate buffer containing 0.1M of NaCl to obtain new elulates of protein peak.

The claimed invention as recited in claims 28 (h), 31(c5) and 33 (r) differs from the reference only that the preparation of IgY against dental carries bacteria by eliminating bacteria by 0.22μm membrane filtration.

The claimed invention as recited in claims 30(c1), 31(c1) and 32(i) differs from the references only that the preparation step (c) comprises the step of evenly stirring said egg yolks and diluting with 4-6 fold of distilled water to obtain a diluted yolk solution.

The '782 patent teaches antibody against Streptococcus mutans generated from bovine milk can inhibit dental caries (See entire document). The '782 patent teaches cultivating S. mutans such as strains AHT, BHT, 10499 and 6715 separately in culture for 48 hours (2 days) at 37 °C, collecting the bacteria by centrifugation, wash bacteria 5 times with distilled water or physiological saline solution, and heat killed bacteria by heating at 56 °C for two hours, mixing the different strains at 1:1 ratio by suspending the heat killed bacteria in physiological saline solution for immunization (See column 3, lines 16-66, in particular).

The '054 patent teaches a method of preparing egg immunoglobulin Y (IgY) against bacteria *Streptococcus mutans* (See column 8, line 26, in particular) wherein the method steps

comprises immunizing hens with a mixture of bacteria such as *Streptococcus mutans* by injection each time at two weeks intervals (See column 8, lines 9-66, in particular), collecting the eggs after hyperimmunization, extracting crude IgY by water dilution such as diluting the separated egg yolk with 5-30 times deionized water, preferably with 4-6 fold of distilled water (See column 5, lines 38-40, column 2, line 24, in particular), adjusting the diluted yolk solution to pH about 4-6 (See column 5, lines 48-49, in particular), standing the diluted yolk solution at 3-4 °C for at least 2 hr for phase separation (See column 2, line 24, in particular), centrifuging the diluted yolk solution at high speed at about 2500-30,000 rpm to obtain a supernatant (See column 5, line 44, in particular), concentrating the supernatant which is the crude IgY by ultrafiltration (See column 5 line 65-68 bridging column 6, lines 1-2, Example 5, in particular). Following ultrafiltration, the partially pure IgY retentate can be dried by lyophilization (freeze dry) or spray dry (See column 12, example 12, in particular) and/or further purified by sequential ion exchange chromatography such as DEAE column chromatography (See entire document, column 10 line 69 bridging column 11; column 6, line 15; column 6 line 55, Fig 1, in particular), and cation exchange chromatography such as Sephadex column chromatography using the appropriate buffer for the specific column (See column 11, Example 6, example 8, in particular). For ion exchange chromatography, the column matrix that is suitable for large scale IgY purification includes DEAE (diethylaminoethyl)-Sepharose or DEAE-Sephadex wherein the IgY is eluted with DEAE ion exchange buffer (eluant) which is a sodium phosphate buffer containing about 0.01-0.4M NaCl as the final salt concentration (See entire document, column 5 line 49, in particular). Other suitable anion-exchange chromatography materials as well as the selection of using these materials are known to those ordinary skilled in the art (See column 6, line 55, in particular). The '054 patent further teaches egg yolk is a very good source of specific antibodies, the advantages of IgY antibody production is about 100-150 mg/egg and maintenance of higher levels of specific antibodies is relatively easy (See column 1, lines 34-54, in particular). The '054 patent teaches egg yolk (IgY) is a very good source of specific antibodies and that production and maintenance of high levels of specific antibodies is relatively easy (See column 1, lines 34-46, in particular).

Akita *et al* teach a preparation method of extracting egg IgY immunoglobulin by water dilution with six-fold of water, adjusting the pH 5.0 to 5.2, let it stands for at least 2 hr before high speed centrifugation (See entire document, page 629 Materials and Methods) to yield 100mg pure IgY per egg by a combination of ultrafiltration, gel filtration with Sephacryl S-200 using 0.1M phosphate buffer at pH 7.0 and DEAE-Sephacel anion exchange chromatography

equilibrate with the appropriate starting buffer (See entire document, Materials and Methods, page 630, in particular) wherein the choice of column depends on the amount of IgY to be purified. Furthermore, Akita *et al* teach that the optimal dilution of egg yolk with six-fold of water at a pH 5.0 and incubation time of 6 hour at 4 °C gave an IgY recovery of 93-96% (See page 632, right column second paragraph). Akita *et al* teach that the use of gel filtration or anion exchange as the final steps should be most efficient. The advantages of this protocol are that the procedure is simple, rapid and produces high yields of active IgY (See page 633, right column last paragraph, in particular).

The '376 patent teaches purification of immunoglobulin such as anti-B2M simply by initial immunosorbent purification using gel filtration on material such as Sephadex (dextran based) follows by a gel filtration step using material such as Sephadex G-200 to separate the immunoglobulin and impurity on the basis of molecular weight (See column 5, line 11-32, lines 61-68, in particular). The '376 patent further teaches the "best results are obtained with material such as those marketed under the trade names Sephadex G-200" using phosphate buffered saline (See column 5, lines 65-68, column 10, line 39-40, in particular).

The '094 patent teaches sterilizing immunoglobulin by filtration through a 0.22 μm membrane for intravenous injection (See column 10, lines 60-62, Fig 1, claims of '094, in particular). The '094 patent teaches that the advantages of filtration through a 0.22 μm membrane are (1) simplicity, (2) speed, (3) the method can be easily scale up and (4) the products are free from virus and can be isolated in higher yields (See column 3, lines 1-14, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine S. mutans c and S. mutans d as taught by Chang e*t al* or the '782 patent as immunogen for preparing IgY against dental carries as taught by Chang et al, the '782 patent and the '054 patent by extracting the crude IgY from the eggs using the water dilution method as taught by the '054 patent or Akita *et al* and follows by gel filtration chromatograph such as DEAE-Sephadex chromatography as taught by the '054 patent and the "DEAE-Sephadex A50" column chromatography as taught by the '376 patent and eliminating the residual bacteria in the preparation by 0.22μm membrane filtration as taught by the '094 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Chang e*t al* teach IgY antibody against both S mutans c and d must be applied simultaneously to

effectively prevent the human dental caries (See page 65, Conclusion, page 63, column 1, second to the last paragraph, in particular) since the immunodominant sugars in the cell walls of S mutans a, c, e, and f are glucose-glucose while those in the cell walls of S mutans B, d and g are glalactose (See page 63, column 1, fourth paragraph, in particular); human dental caries is mainly (over 70%) caused by S. mutans c followed by S. mutans d (See page 63, column 1, second to the last paragraph, in particular). The '054 patent teaches egg yolk (IgY) is a very good source of specific antibodies and that production and maintenance of high levels of specific antibodies is relatively easy (See column 1, lines 34-46, in particular). Akita *et al* teach that the use of gel filtration or anion exchange as the final steps of IgY preparation should be most efficient. The advantages of gel filtration are simple, rapid and produces high yields of active IgY (See page 633, right column last paragraph, in particular). The '376 patent teaches purification of any immunoglobulin by initial immunosorbent purification using gel filtration on material such as Sephadex (dextran based) follows by a gel filtration step using material such as Sephadex G-200 to separate the immunoglobulin and impurity on the basis of molecular weight (See column 5, line 11-32, lines 61-68, in particular). The '376 patent further teaches the "best results are obtained with material such as those marketed under the trade names Sephadex G-200" using phosphate buffered saline (See column 5, lines 65-68, column 10, line 39-40, in particular). The '094 patent teaches that the advantages of filtration through a 0.22 μm membrane are (1) simplicity, (2) speed, (3) the method can be easily scale up and (4) the products are free from virus and can be isolated in higher yields (See column 3, lines 1-14, in particular). Claims 28(a4) and 32(d) are included in this rejection because it is within the purview of one ordinary skill in the art at the time the invention was made to include S mutans d as immunogen since Chang e*t al* teach the immunodominant sugars in the cell walls of S mutans a, c, e, and f are glucose-glucose while those in the cell walls of S mutans B, d and g are glalactose and antibody to both S. mutans c and d should be applied to both simultaneously in order to be effectively prevent human dental caries (See page 63, column 1, fourth paragraph, and page 65, column 2, Conclusion, in particular). The recitation of mixing mutans type c and type d in a ratio of 2:1 is an obvious variation in the teachings of Chang et al who teaches human dental caries is mainly (over 70%) caused by S. mutans c followed by S. mutans d which suggests that the antibody against c and d must be applied simultaneously to effectively prevent the human dental caries (See page 63, column 1, second to the last paragraph, in particular). Claims 29(b3) and 32(h) are included in this rejection because taking out the yolk by sieve is well within the purview of one skill in the art

at the time the invention was made. Claims 30(c1), and 31(c1) are included in this rejection because the '054 patent and Akita et al teach diluting the yolks with 5-31 fold water, which includes the claimed diluting with 4-6 fold-distilled water. Claims 30(c2) and 31(c2) are included in this rejection because the reference pH about 4-6 includes the claim pH 4.5-6.5. Claims 30(c3) and 31(c3) are included in this rejection because standing yolk solution for 20-30 hours for phase separation is within the purview of one ordinary skill in the art at the time the invention was made to practice the claimed invention because the '054 patent teaches standing the diluted yolk solution at 3-4 °C for a minimum of at least 2 hr or longer for phase separation (See column 2, line 24, in particular). Claims 30(c4) and 30(c4) are included in this rejection because centrifugation of any solution to obtain a supernatant is within the purview of purview of one ordinary skill in the art at the time the invention was made to practice the claimed invention as taught by Chang *et al.*

Applicants' arguments filed 5/22/03 have been fully considered but are not found persuasive.

Applicants' position is that (1) regarding claims 28(a1) and 31(a), Chang et al teach cultivating S. mutans c for 18 hours, not 2 to 3 days of the present invention. The '782 patent teach cultivating S mutans for 48 hours, not make out c and d; other cited arts do not teach this step. (2) Regarding claims 28(a2) and 31(b), Chang et al teach to treat with 0.5 formalin for 24 hours. The present invention need not to treat with formalin. Similar with '782 patent, the subject matter of the '782 patent is to immunize cow, not hens. The other cited arts do not teach this step. (3) Regarding claims 28(a3) and 31(c), Chang et al teach to wash with sterile saline containing 0.5% formalin. The present invention is washing with PBS which containing no formalin. And then heating at 50-60 °C for 25 to 35 minutes. Similar with the '782 patent, but the subject matter of the '782 patent is to immunize to immunize cow, not hens. The other cited arts do not teach this step. (4) Regarding claims 29(b1) and 31(f), Chang et al teach to inject once a week for 4 weeks. The present invention is 3 hypodermic injections, each time at two weeks intervals. (5) Chang et al teach 70% of human dental caries caused by c and suggest apply c and d simultaneously, not make out the ratio of c and d while the present invention makes out the ratio as 2:1. (6) none of the cited art teaches adding Freund's adjuvant equal to total volume of streptococcus mutants with high-speed homogenizer. (7) Chang et al teach to inject once a week for 4 weeks whereas the present invention requires 3 hypodermic injections. (8) none of the cited art teaches collecting and sterilizing said eggs from 20th day after the first hypodermic injection.

(9) the present invention teaches to take out yolk by sieve and the cited arts do not teach the usage of sieve either. (10) Chang et al teach high methoxy pectin method follows by gel filtration while the present invention is water dilution. (11) none of the cited references teaches adjusting diluted yolk solution to pH 4.5 to 6.5. (12) Chang et al teach standing the diluted yolk solution at 3-5 °C for 30 minutes and not for 20-30 hours as claimed. (13) none of the references teach centrifugation to get supernatants as recited in steps 30c4 in claim 30 and claim 31(I). (14) Chang et al teach to filter through a No 2 filter, Chang et al do not teach concentrating supernatant by ultrafiltration. (15) Chang et al teach gel filtration with Sephacryl S-300, and do not teach the use of "DEAE-Sephadex A50" and he '054 patent teach purified by DEAE-SPW, DEAD-Sepharose, DEAE-Sepherodes, DEAD-650 or DE92 etc, but not the use of "DEAE-Sephadex A-50" or "DEAE-Sephadex". (16) the '376 patent teaches the uses of Sephadex G200 for isolating IgG and not for preparing IgY. (17) the '094 patent teaches the use of 0.22μm to prepare IgG from blood plasma of animal or human and not for preparing IgY. (18) there is no suggestion to combine the references. (19) The modification does not provide the following features: a long period of validity, high titer of antibody, good effect of restraining activity of streptococcus mutants, no chemical pollution and comprehensively utility of remains, low preparation cost, implementation probability, high purity, and dental caries preventing combinations with IgY.

In response to applicant's argument that Chang et al teach cultivating S. mutans c for 18 hours, not 2 to 3 days of the present invention, it is within the purview of one ordinary skill in the art at the time the invention was made to cultivate bacteria such as streptococcus mutans such as c or d in a culture medium for as long as one desire such as for 2 to 3 days to obtain the desire concentration for use as immunogen. The '782 patent teaches cultivating S. mutans such as strains AHT, BHT, 10499 and 6715 separately in culture for 48 hours (2 days) at 37 °C, collecting the bacteria by centrifugation, wash bacteria 5 times with distilled water or physiological saline solution, and heat killed bacteria by heating at 56 °C for two hours, mixing the different strains at 1:1 ratio by suspending the heat killed bacteria in physiological saline solution for immunization (See column 3, lines 16-66, in particular). Thus, the "2 to 3 days" is an obvious variation of the teachings of the '782 patent.

In response to applicant's argument that Chang et al teach to treat with 0.5 formalin for 24 hours and the present invention need not to treat with formalin, the '782 patent teaches cultivating

S. mutans separately in culture for 48 hours (2 days) at 37 °C, collecting the bacteria by centrifugation, wash bacteria 5 times with distilled water or *physiological saline solution*, and heat killed bacteria by heating at 56 °C which is within 50-60°C (See column 3, lines 16-66, in particular).

In response to applicant's argument that Chang et al teach 70% of human dental caries caused by c and suggest apply c and d simultaneously, not make out the ratio of c and d while the present invention makes out the ratio as 2:1, Chang e*t al* teach human dental caries is mainly (over 70%) caused by S. mutans c followed by S. mutans d and that the antibody against c and d must be applied simultaneously to effectively prevent the human dental caries (See page 63, column 1, second to the last paragraph, in particular). The ratio of S. mutans c such as (71%) to d (29%) is about 2:1 ratio.

In response to applicant's argument that none of the cited art teaches adding Freund's adjuvant equal to total volume of streptococcus mutants with high speed homogenizer, Chang e*t al* teach adding adjuvant such as Freund's incomplete adjuvant to equal volume of S mutans and mixed homogenously prior to immunizing hens by hypodermic needle injection of S mutans 1 x 10^9 at CFU/ml each time at once a week for 4 weeks intervals to obtain eggs with active antibody (See page 61 Immunization of Hens, in particular).

In response to applicant's argument that Chang et al teach to inject once a week for 4 weeks whereas the present invention requires 3 hypodermic injections, each time at two weeks intervals, the '054 patent teaches injection of *Streptococcus mutans* each time at two weeks intervals (See column 8, lines 9-66, in particular). The booster shot for inducing antibody response is within the purview of one ordinary skill in the immunology art at time the invention was made. Further, the number of injection such as 3 injection at two weeks intervals is an obvious variation of the combined teachings of Chang et al and the '054 patent.

In response to applicant's argument that none of the cited art teaches collecting and sterilizing said eggs from 20th day after the first hypodermic injection, Chang e*t al* teach that active antibody against S mutans begins to climb in the third week which is 20 days after immunization and last about 13 weeks and then decreased gradually to the 23rd week (See Fig 1, page 63, Effect of Immunization Route on Antibody Activity, in particular). The '054 patent teaches collecting the eggs after hyperimmunization. Likewise, the method of Chang inherently also requires collecting the eggs after hyperimmunization prior to purification. The eggs obviously are sterile since the egg shelve have not been cracked.

In response to applicant's argument that the present invention teaches to take out yolk by sieve and the cited arts do not teach the usage of sieve either, it is within the purview of one ordinary skill in the art at the time the invention was made to use a strainer such as a sieve to separate any solid material from liquid material such as a yolk from the egg white.

In response to applicant's argument that Chang teach high methoxy pectin method follows by gel filtration while the present invention is water dilution, Akita *et al* teach a preparation method of extracting egg IgY immunoglobulin by water dilution (See entire document, page 629 Materials and Methods). Likewise, the '054 patent teaches a method of preparing egg immunoglobulin Y (IgY) against bacteria *Streptococcus mutans* using the water dilution method such as diluting the separated egg yolk with 5-30 times deionized water, preferably with 4-6 fold of distilled water (See column 5, lines 38-40, column 2, line 24, in particular).

In response to applicant's argument that none of the cited references teaches adjusting diluted yolk solution to pH 4.5 to 6.5, Akita *et al* teach a preparation method of extracting egg IgY immunoglobulin by water dilution with six-fold of water, adjusting the pH 5.0 to 5.2, which is within the claimed pH of 4.5 to 6.5 (See entire document, page 629 Materials and Methods). Further, the '054 patent teaches a method of preparing egg immunoglobulin Y (IgY) against bacteria *Streptococcus mutans* (See column 8, line 26, in particular) by water dilution such as diluting the separated egg yolk with 5-30 times deionized water, preferably with 4-6 fold of distilled water (See column 5, lines 38-40, column 2, line 24, in particular), adjusting the diluted yolk solution to pH about 4-6 (See column 5, lines 48-49, in particular), standing the diluted yolk solution at 3-4 °C for at least 2 hr for phase separation (See column 2, line 24, in particular).

In response to applicant's argument that Chang et al teach standing the diluted yolk solution at 3-5 C for 30 minutes and not for 20-30 hours as claimed, the '054 patent teaches a method of preparing egg immunoglobulin Y (IgY) against bacteria *Streptococcus mutans* (See column 8, line 26, in particular) by water dilution such as diluting the separated egg yolk with 5-30 times deionized water, preferably with 4-6 fold of distilled water (See column 5, lines 38-40, column 2, line 24, in particular), adjusting the diluted yolk solution to pH about 4-6 (See column 5, lines 48-49, in particular), standing the diluted yolk solution at 3-4 °C for at least 2 hr for phase separation (See column 2, line 24, in particular), which encompasses 20-30 hours. Further, standing the dilution yolk solution for as long as it takes such as two to three days is within the

purview of one ordinary skill in the art at the time the invention was made. Not only it is an obvious variation of the teachings of the '054 patent but also it is the convenience for the practitioner.

In response to applicant's argument that none of the references teach centrifugation to get supernatants as recited in steps 30c4 in claim 30 and claim 31(I), the '054 patent teaches centrifuging the diluted yolk solution at high speed at about 2500-30,000 rpm to obtain a supernatant (See column 5, line 44, in particular). Akita *et al* teach a preparation method of extracting egg IgY immunoglobulin by water dilution with six-fold of water, adjusting the pH 5.0 to 5.2, let it stands for at least 2 hr before high speed centrifugation (See entire document, page 629 Materials and Methods). The duration such as 20 to 30 minutes of centrifugation is within the purview of one ordinary skill in the art at the time the invention because the main objective of centrifugation is to separate the supernatant from the solid as evidence by Chang et al, Akita et al and the '054 patent. Further, The teachings of a species such as high-speed centrifugation anticipate a genus such as centrifugation.

In response to applicant's argument that Chang et al teach to filter through a No 2 filter, Chang et al do not teach concentrating supernatant by ultrafiltration. However, the '054 patent teaches concentrating the supernatant which is the crude IgY by ultrafiltration (See column 5 line 65-68 bridging column 6, lines 1-2, Example 5, in particular).

In response to applicant's argument that Chang et al teach gel filtration with Sephacryl S-300, and do not teach the use of "DEAE-Sephadex A50" and he '054 patent teach purified by DEAE-SPW, DEAD-Sepharose, DEAE-Sepherodes, DEAD-650 or DE92 etc, but not the use of "DEAE-Sephadex A-50" or "DEAE-Sephadex", the '376 patent teaches purification of immunoglobulin such as anti-B2M simply by initial immunosorbent purification using gel filtration on material such as Sephadex (dextran based) follows by a gel filtration step using material such as Sephadex G-200 to separate the immunoglobulin and impurity on the basis of molecular weight (See column 5, line 11-32, lines 61-68, in particular). The '376 patent further teaches the "best results are obtained with material such as those marketed under the trade names Sephadex G-200" using phosphate buffered saline (See column 5, lines 65-68, column 10, line 39-40, in particular). Further, the '054 patent teaches that suitable chromatography materials for

separating IgY are known to those of ordinary skill in the art (See column 6, line 55-28, in particular).

In response to applicant's argument that the '376 patent teaches the uses of Sephadex G200 for isolating IgG and not for preparing IgY, the principle of separating any immunoglobulin such as IgG or IgY applied based on molecular weight as taught by the '376 patent applied to any immunoglobulin such as IgG or IgY (See column 5, line 11-32, lines 61-68, in particular). It is within the purview of one ordinary skill in the art to use the appropriate column as taught by any of the cited references mentioned above to separate any immunoglobulin based on molecular weight as taught by the '376 patent or by charge as taught by the '054 patent. Further, the "Sephadex G200" and "DEAE-Sephadex A50" are trademark or trade name; the claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. The formula or characteristics of the product may change from time to time and yet it may continue to be sold under the same trademark or trade name.

In response to applicant's argument that the '094 patent teaches the use of 0.22μm to prepare IgG from blood plasma of animal or human and not for preparing IgY, the '094 patent teaches sterilizing immunoglobulin by filtration through a 0.22 μm membrane for intravenous injection (See column 10, lines 60-62, Fig 1, claims of '094, in particular). The '094 patent teaches that the advantages of filtration through a 0.22 μm membrane are (1) simplicity, (2) speed, (3) the method can be easily scale up and (4) the products are free from virus and can be isolated in higher yields (See column 3, lines 1-14, in particular). It is within the purview of one ordinary skill in the art at the time the invention was made to use 0.22μm to sterilize any solution whether it is immunoglobulin IgG or IgY, especially the preparation is for human consumption.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See In re Fine 5 USPQ2d 1596 (Fed. Cir 1988) and In re Jones 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Chang *et al* teach a preparation method of immunoglobulin Y (IgY) against dental caries bacteria the high methoxy

pectin method; the '054 patent also teaches preparing egg immunoglobulin Y (IgY) against bacteria *Streptococcus mutans* using the water dilution method. The teachings of the '054 patent, and Anita et al indicate the success in purifying IgY using the water dilution method follows by various column chromatography known to one ordinary skill in the art. It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine S. mutans c and S. mutans d as taught by Chang e*t al* or the '782 patent as immunogen for preparing IgY against dental carries as taught by Chang et al, the '782 patent and the '054 patent by extracting the crude IgY from the eggs using the water dilution method as taught by the '054 patent or Akita *et al* and follows by gel filtration chromatograph such as DEAE-Sephadex chromatography as taught by the '054 patent and the "DEAE-Sephadex A50" column chromatography as taught by the '376 patent and eliminating the residual bacteria in the preparation by 0.22μm membrane filtration as taught by the '094 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Chang e*t al* teach IgY antibody against both S mutans c and d must be applied simultaneously to effectively prevent the human dental caries (See page 65, Conclusion, page 63, column 1, second to the last paragraph, in particular) since the immunodominant sugars in the cell walls of S mutans a, c, e, and f are glucose-glucose while those in the cell walls of S mutans B, d and g are glalactose (See page 63, column 1, fourth paragraph, in particular); human dental caries is mainly (over 70%) caused by S. mutans c followed by S. mutans d (See page 63, column 1, second to the last paragraph, in particular). The '054 patent teaches egg yolk (IgY) is a very good source of specific antibodies and that production and maintenance of high levels of specific antibodies is relatively easy (See column 1, lines 34-46, in particular). Akita *et al* teach that the use of gel filtration or anion exchange as the final steps of IgY preparation should be most efficient. The advantages of gel filtration are simple, rapid and produces high yields of active IgY (See page 633, right column last paragraph, in particular). The '376 patent teaches purification of any immunoglobulin by initial immunosorbent purification using gel filtration on material such as Sephadex (dextran based) follows by a gel filtration step using material such as Sephadex G-200 to separate the immunoglobulin and impurity on the basis of molecular weight (See column 5, line 11-32, lines 61-68, in particular). The '376 patent further teaches the "best results are obtained with material such as those marketed under the trade names Sephadex G-200" using

phosphate buffered saline (See column 5, lines 65-68, column 10, line 39-40, in particular). The '094 patent teaches that the advantages of filtration through a 0.22 μm membrane are (1) simplicity, (2) speed, (3) the method can be easily scale up and (4) the products are free from virus and can be isolated in higher yields (See column 3, lines 1-14, in particular). The strongest rationale for combining reference is a recognition, expressly or implicitly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent that some advantage or expected beneficial result would have been produced by their combination In re Sernaker 17 USPQ 1, 5-6 (Fed. Cir. 1983) see MPEP 2144.

In response to features in the last item, the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985).

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

8. Claims 28-33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 28 and 32 contain the trademark/trade name "DEAE-Sephadex A50" and "Sephadex G200". Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade name is used to identify/describe the column and, accordingly, the identification/description is indefinite.

9. No claim is allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

11. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

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